Quick guide

JNK

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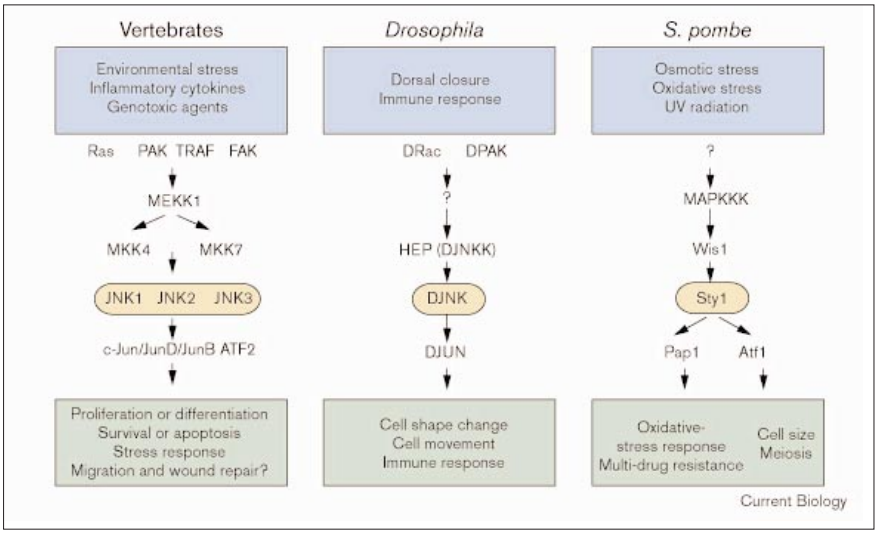
What is it? As its full name suggests, Jun N-terminal kinase (JNK, pronounced 'junk') is an enzyme that phosphorylates the amino-terminal domain of the Jun transcription factors. JNK is a serine/threonine kinase, a member of the extensive family of MAP kinase proteins critical for signal transduction pathways.

Also known as… stress-activated protein kinase (SAPK), because it is activated in many cells in response to cellular stress, such as treatment with UV radiation or genotoxic agents.

What does it do? JNK is important for sending signals from the cell membrane to nuclear transcription factors, increasing their ability to activate transcription. JNK signalling has been implicated in cell growth, oncogenic transformation, cell differentiation and cell death. Stimuli that activate JNK include growth factors, cytokines and just about any kind of stress (see Figure). JNK can be turned off by dual specificity MAPK phosphatases (MKPs), which often function in a negative feedback loop.

How many JNK proteins are there? Lots. In mammals there are three *jnk* genes: *jnk1*, *jnk2* and *jnk3*. The *jnk1* and *jnk2* genes are widely expressed, whereas *jnk3* is restricted to the brain, heart and testis. Elaborate alternative splicing generates at least 10 different JNK isoforms, which might differ in their substrate specificity.

What are its substrates? JNK substrates include all three Jun proteins (c-Jun, JunB and JunD) and the related ATF2 transcription factor. Recently JNK has also been shown to phosphorylate Ets transcription factors such as Elk-1, and even the tumour suppressor p53.



Pathways of JNK activation and activity in vertebrates, *Drosophila* and *S. pombe*. In vertebrates, JNK is activated by dual phosphorylation on specific Ser/Thr and Tyr residues by two upstream MAP kinase kinases, MKK4 and MKK7. The MKKs themselves are activated by MAPKKK proteins (MEKK1). These cascades of phosphorylation events can be set in motion by anything from growth factor receptors, to UV radiation, to TNF receptors. The signals pass via small GTPases (such as Ras and Rac), adaptor proteins (TRAF) or kinases (PAK and FAK). See text for details of the *Drosophila* and *S. pombe* pathways.

What happens without it? Mice lacking any single *jnk* gene are viable — until they encounter stress. For example, *jnk3*$^{-/-}$ mice seem to be fine but, when treated with an excitotoxin, they show reduced stress-induced apoptosis of neurons in the brain. Studies of knockout mice indicate that the *jnk1* and *jnk2* genes are important for efficient activation of T lymphocytes and the balance between Th1/Th2 immune responses to pathogenic stress. The fact that double knockout *jnk1*$^{-/-}$*jnk2*$^{-/-}$ embryos have defects in neural tube closure shows that there is genetic redundancy between the *jnk* genes.

Where else is it found? In *Drosophila* there is only one JNK, DJNK; interestingly, it's also involved in the immune response and in embryonic dorsal closure. The JNK signalling pathway is highly conserved between mammals and insects (see Figure), and the *Drosophila* pathway might offer a genetic model for mammalian wound healing — an analogous morphogenesis event. Even the fission yeast *Schizosaccharomyces pombe* responds to oxidative and osmotic stress with the SAPK Sty1. Sty1 is the substrate of the yeast MAPKK Wis1, and phosphorylates the Jun-like proteins Pap1 and Atf1 (see Figure).

Things to remember… Don't panic when you look at those spiderwebs of signal transduction pathways. As long as your JNKs are intact, you're prepared for any stressful situation.

Where can I find out more?

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Leppa S, Bohmann D: **Diverse functions of JNK signaling and c-Jun in stress response and apoptosis.** *Oncogene* 1999, **18:**6158-6162.

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